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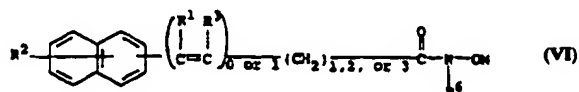
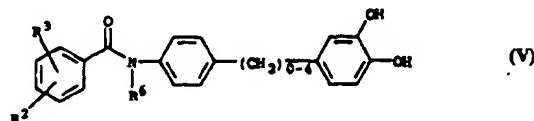
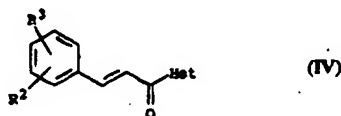
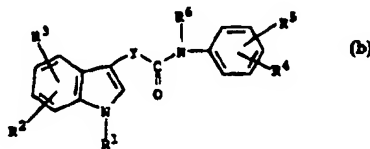
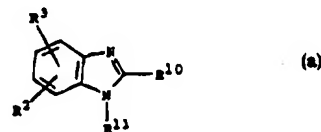
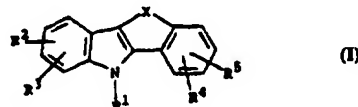
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<p>(21) International Application Number: PCT/US96/14242 (22) International Filing Date: 5 September 1996 (05.09.96) (30) Priority Data: 60/005,201 5 October 1995 (05.10.95) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CORNICELLI, Joseph, Anthony [US/US]; 2878 E. Eisenhower Parkway, Ann Arbor, MI 48108 (US). PADIA, Janak, Khimchand [US/US]; 3802 Fieldcrest Lane, Ypsilanti, MI 48197 (US). TAIT, Bradley, Dean [US/US]; 8431 Congress Drive, Canton, MI 48187 (US). TRIVEDI, Bharat, Kalidas [IN/US]; 36955 Aldergate Court, Farmington Hills, MI 48335 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.</p>		<p>(81) Designated States: AU, CA, EE, JP, LT, LV, MX, NZ, SI, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>

(54) Title: METHOD FOR TREATING AND PREVENTING INFLAMMATION AND ATHEROSCLEROSIS

(57) Abstract

Inhibitors of 15-lipoxygenase (15-LO) are useful to treat and prevent inflammation or atherosclerosis. Preferred inhibitors have a ratio of 5-LO to 15-LO inhibitory activity of at least about 10 or more. Typical 15-LO inhibitors have the formulas (I), (a), (b), (IV), (V), and (VI) wherein R¹, R², R³, and R⁶ independently are hydrogen, alkyl, halo, cyano, nitro, alkoxy, amino, alkoxy carbonyl, carboxamido, alkoxy methyl and aminomethyl, and M is a cation; R¹⁰ is halo, amine, phenyl or substituted phenyl; R¹¹ is hydrogen, SO₂R¹², alkyl, phenyl, substituted phenyl, or Het; and Het is a heterocyclic ring.



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METHOD FOR TREATING AND PREVENTING INFLAMMATION
AND ATHEROSCLEROSIS

This invention concerns a method for treating and preventing inflammation or atherosclerosis in mammals by administering a compound which is an inhibitor of the enzyme 15-lipoxygenase (15-LO).

BACKGROUND OF THE INVENTION

Atherosclerosis is a multifactorial disease characterized by excessive intracellular lipid deposition in macrophages, leading to formation of foam cells. The accumulation of lipid-loaded foam cells in the subendothelial space leads to formation of fatty streaks, which are the early atherosclerotic lesions. Oxidative modification of lipids, specifically low-density lipoprotein, has been implicated as a major process in foam-cell formation.

Lipoxygenases are nonheme iron-containing enzymes that catalyze the oxygenation of certain polyunsaturated fatty acids such as lipoproteins. Several different lipoxygenase enzymes are known, each having a characteristic oxidation action. One specific lipoxygenase, namely 15-LO, has been detected in atherosclerotic lesions in mammals, specifically rabbit and man. The enzyme, in addition to its role in oxidative modification of lipoproteins, is important in the inflammatory reaction in the atherosclerotic lesion. Indeed, 15-LO has been shown to be induced in human monocytes by the cytokin IL-4, which is known to be implicated in the inflammatory process.

Another class of lipoxygenase enzymes is 5-lipoxygenase (5-LO). While this enzyme causes

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oxidation of unsaturated fatty acids, it primarily is responsible for inserting oxygen on position 5 of arachidonic acid. Other lipoxygenases are known; one of the most common and abundant being 12-lipoxygenase (12-LO).

We have now found that inhibitors of 15-LO are especially useful to prevent and treat inflammation and atherosclerosis. While there are several lipoxygenase enzymes, specific inhibition of 15-LO is critical in the inflammatory and atherosclerosis process. All that is required according to this invention is to administer a 15-LO inhibitor, and especially one that is a specific 15-LO inhibitor.

Several classes of organic compounds are 15-LO inhibitors.

Tetracyclic indole and benzopyranoindole compounds are potent 15-LO inhibitors. United States Patent Number 3,388,133 describes benz[b]indolo[2,3-d]-thiopyrano and pyrylium salts as antibacterial and antifungal agents. United States Patent Number 4,132,714 describes a process for making chromenoindoles, which are said to be useful as color-forming agents. United States Patent Number 4,797,495 discloses a wide variety of benzocarbazoles which are said to be antitumor agents. Similarly, benzimidazoles are well known as antiviral agents. United States Patent Number 4,293,558 describes various 1-thiazolinyl-2-aminobenzimidazoles, and United States Patent Number 4,243,813 describes 1-sulfonyl-benzimidazoles. None of those compounds have been described as inhibitors of 15-LO, and none have been utilized in treating inflammation or atherosclerosis. All of these compounds are 15-LO inhibitors and can be employed in the method of this invention.

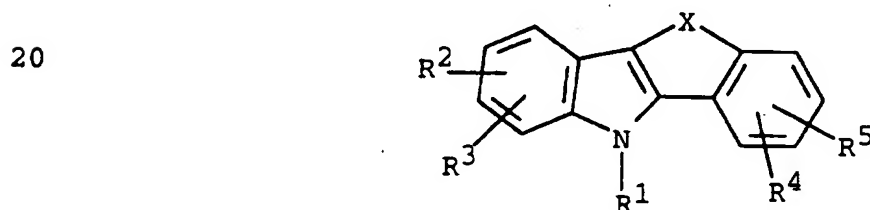
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We have now discovered that compounds which are effective inhibitors of 15-LO are useful in treating and preventing inflammation and atherosclerosis.

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SUMMARY OF THE INVENTION

This invention provides a method for treating and preventing inflammation or atherosclerosis in mammals comprising administering an effective amount of a 15-LO inhibitor. The invention preferably employs a specific 15-LO inhibitor. In a preferred embodiment, the 15-LO inhibitor is a benzopyranoindole or related compound as described in United States Patent Number 3,388,133, 4,132,714, and 4,797,495, which are incorporated herein by reference. Especially preferred 15-LO inhibitors have Formula I



I

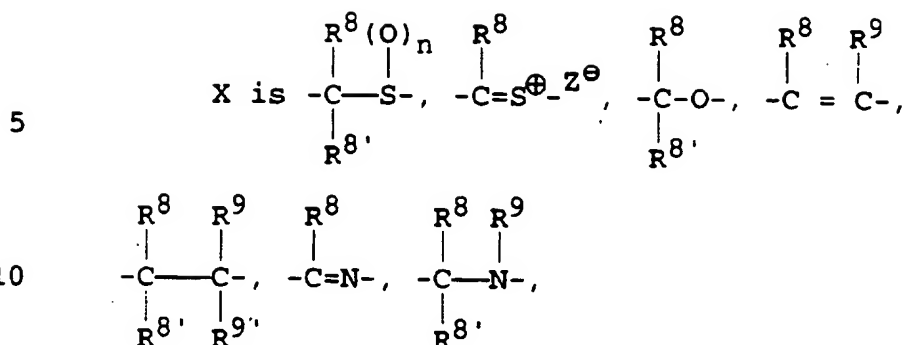
25 wherein:

R^1 is hydrogen or C_1 - C_6 alkyl;

30 R², R³, R⁴, and R⁵ independently are hydrogen, C₁-C₆ alkyl, nitro, halo, CN, OR⁶, NR⁶R⁷, -CO₂R⁶, CONR⁶R⁷, CH₂OR⁶, or CH₂NR⁶R⁷, and R² and R³, and R⁴ and R⁵, when attached to adjacent ring atoms, can be -(CH₂)₃ or 4-;

in which R⁶ and R⁷ independently are hydrogen, C₁-C₆ alkyl, phenyl or benzyl, and when taken together with the nitrogen to which they are attached, R⁶ and R⁷ can complete a cyclic ring having from 3 to 7 carbon atoms;

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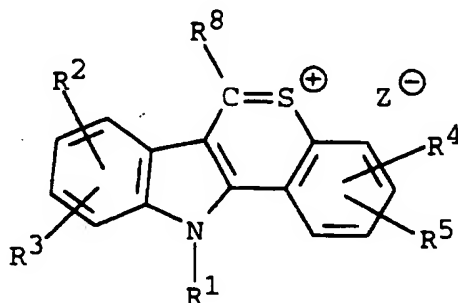


15 in which R^8 , $\text{R}^{8'}$, R^9 , and $\text{R}^{9'}$ independently are hydrogen or C_1 - C_6 alkyl, n is 0, 1, or 2, and Z^- is an anion, and pharmaceutically acceptable salts thereof.

A preferred method according to this invention employs a compound of the formula

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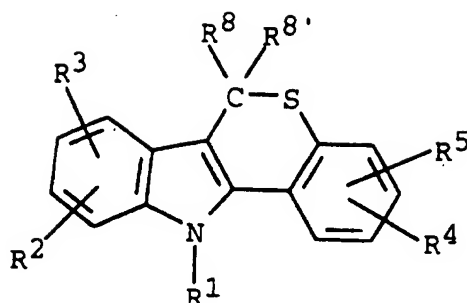
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where R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and Z^- have the above defined meanings. Within this group, preferred compounds to be employed are those wherein R^1 is hydrogen, and one or two of R^2 , R^3 , R^4 , and R^5 are selected from C_1 - C_6 alkyl, halo, nitro, or OR^6 , where R^6 is preferably C_1 - C_6 alkyl.

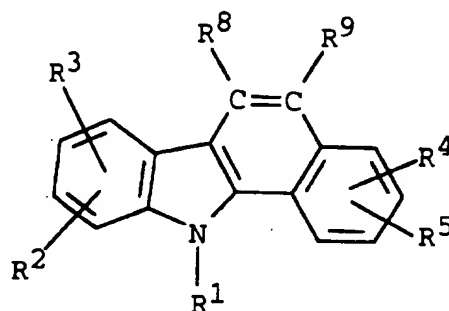
35 Another preferred embodiment utilizes compounds of the formula

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where R¹, R², R³, R⁴, R⁵, R⁸, and R^{8'} are as defined above.

Another preferred method of treatment employs a compound of the formula

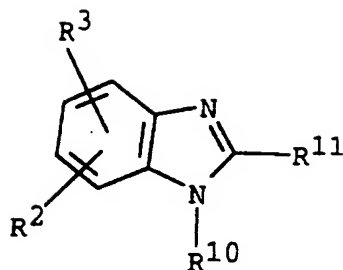


where R¹, R², R³, R⁴, R⁵, R⁸, and R⁹ are as defined above.

Benzimidazole 15-LO inhibitors to be employed in the method of this invention are known and readily available as described in any of the following United States patents, all of which are incorporated herein by reference: 3,853,908; 3,682,952; 3,850,954; 4,118,742; 4,196,125; 4,216,313; and 4,492,708. Additional benzimidazoles are described in the book entitled Benzimidazoles and Congeneric Tricyclic Compounds, P.N. Preston, Ed., John Wiley & Sons, also incorporated herein by reference.

In a preferred embodiment, the 15-LO inhibitor utilized is a benzimidazole having the Formula II

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II

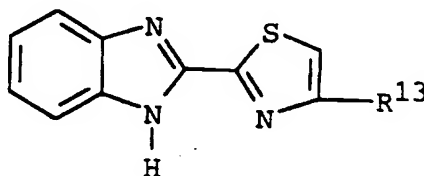
where R^2 and R^3 independently are hydrogen, C_1 - C_6 alkyl, nitro, halo, CN, OR^6 , NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$, and R^2 and R^3 when attached to adjacent ring atoms can be $-(CH_2)_3$ or 4^- ;

R^6 and R^7 are as defined above;

R^{10} is SO_2R^{12} , hydrogen, C_1 - C_6 alkyl, phenyl, or phenyl substituted with 1, 2, or 3 groups selected from halo, CN, OR^6 , C_1 - C_6 alkyl, NR^6R^7 , CO_2R^6 , $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$; and

R^{11} and R^{12} independently are hydrogen, halo, NR^6R^7 , OR^6 , C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl optionally containing an O, N, or S atom, phenyl, or phenyl substituted by 1, 2, or 3 groups selected from halo, CN, OR^6 , C_1 - C_6 alkyl, NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$.

Another preferred method employs a benzimidazole of the formula

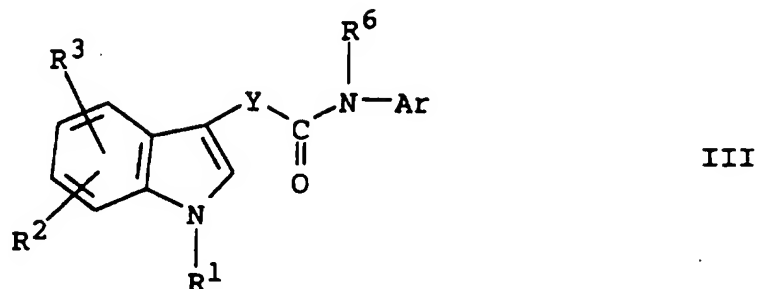


where R^{13} is phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-nitrophenyl, 2,5-dichlorophenyl, 2-furanyl, 2-thienyl, 3-pyridyl, or 4-pyridyl.

In another embodiment, the 15-LO inhibitor utilized is a substituted indole. Typical indoles

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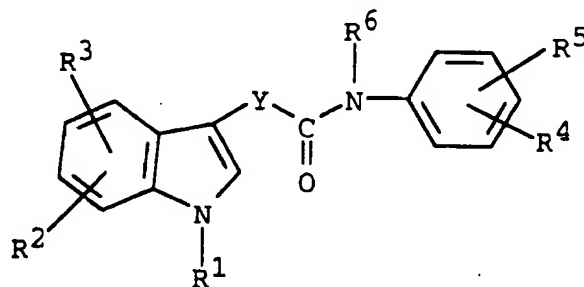
which can be employed include the carbamates and ureas of Formula III



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wherein Y is CH₂, S, O, or NR⁷, and R¹, R², R³, and R⁶ are as defined above, and Ar is phenyl, Het, and phenyl or Het substituted with 1, 2, or 3 groups selected from halo, CN, OR⁶, C₁-C₆ alkyl, NR⁶R⁷, -CO₂R⁶, CONR⁶R⁷, CH₂OR⁶, or CH₂NR⁶R⁷, where Het is a heterocyclic group selected from thiophene, furan, pyrrole, isopyrrole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 1,2,3-oxadiazole, thiazine, pyridine, pyrazine, piperazine, pyrrolidine, piperidine, and pyridazine, and where Het is optionally substituted with phenyl or substituted phenyl, furanyl, thienyl, or pyridyl, and where R⁶ and R⁷ are as defined above. A particularly preferred group of compounds to be employed in the method have the formula

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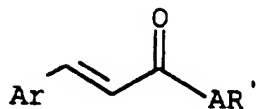
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where R¹, R², R³, R⁴, R⁵, R⁶, and Y are as defined above. Such compounds are described in EP 0150505, which is incorporated herein by reference.

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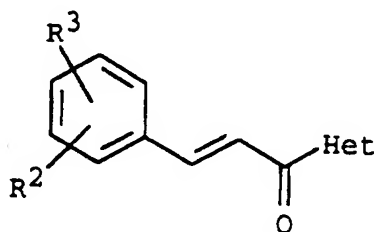
Another class of 15-LO inhibitors which can be utilized in the invention are styrenes having the Formula IV



IV

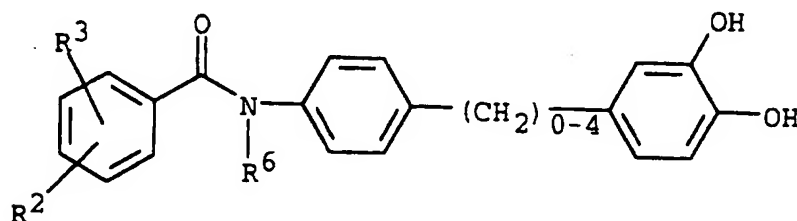
wherein Ar and Ar' independently are phenyl, Het, and phenyl or Het substituted with 1, 2, or 3 groups selected from halo, OR⁶, C₁-C₆ alkyl, NR⁶R⁷, -CO₂R⁶, CONR⁶R⁷, CH₂OR⁶, and CH₂NR⁶R⁷, where R⁶ and R⁷ are as defined above.

A preferred method employs styrene 15-LO inhibitors of the formula



where R², R³, and Het are as defined above.

Another group of 15-LO inhibitors are catacholes, compounds of the Formula V

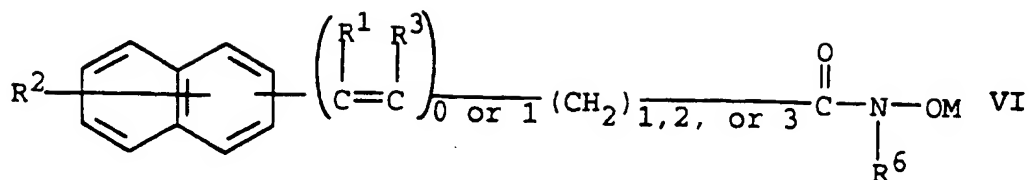


V

wherein R², R³, and R⁶ are as defined above.

Still other 15-LO inhibitors that can be utilized are naphthalenes, especially those of Formula VI

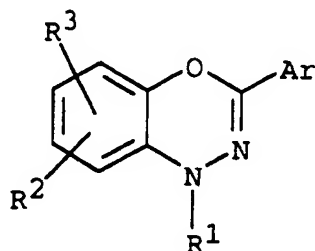
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wherein R^1 , R^2 , R^3 , and R^6 are as defined above, and M is hydrogen or a cation such as sodium, potassium, or calcium. Such compounds are described in United States Patent Number 4,608,390, incorporated herein by reference.

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Another class of 15-LO inhibitors are benzoxadiazines of the general Formula VII



where R^1 , R^2 , R^3 , and Ar are as defined above. Such compounds are described in EP 0410834.

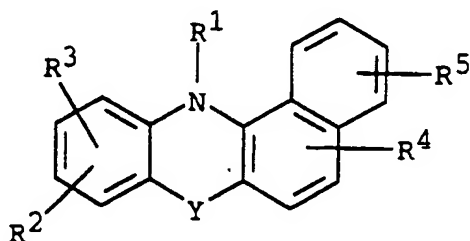
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A preferred embodiment utilizes a benzo[a]phenothiazine which is described in United States Patent Number 4,876,246, incorporated herein by reference. Related 15-LO inhibitors that can be employed are phenothiazone derivatives described in United States Patent Number 4,939,145, incorporated herein by reference.

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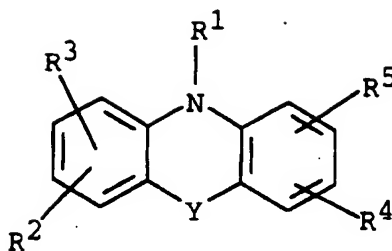
Especially preferred from such classes are compounds having the formulas

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and



where R^1 , R^2 , R^3 , R^4 , R^5 , and Y are as defined above. Such compounds are specifically described in United States Patent Numbers 4,876,246 and 4,939,145.

All that is required to practice the method of this invention is to administer to a mammal a 15-LO inhibiting amount of a 15-LO inhibitor, preferably a specific 15-LO inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

The term " C_1 - C_6 alkyl" means a straight or branched carbon chain such as methyl, ethyl, isopropyl, n-butyl, tert-butyl, sec.-pentyl, 3-methylpentyl, and the like. "Halo" means fluoro, chloro, bromo, and iodo. Ring substituents R^2 , R^3 , R^4 , and R^5 can be OR^6 , where R^6 can be hydrogen or C_1 - C_6 alkyl. Typical groups defined by OR^6 include hydroxy, methoxy, isopropoxy, tert-butoxy, n-hexyloxy, and the like. Ring substituents also are defined by NR^6R^7 , which groups include amino, methylamino, diethylamino, N-methyl-N-isohexylamino, and the like. The ring substituents R^2 , R^3 , R^4 , and R^5 can also be a carboxylic acid, ester, carboxamide, and methylamino group. Typical esters include methoxycarbonyl and ethoxycarbonyl. Typical carboxamide groups include aminocarbonyl, methylamino-carbonyl and N,N-diethylaminocarbonyl. Typical methylamino groups

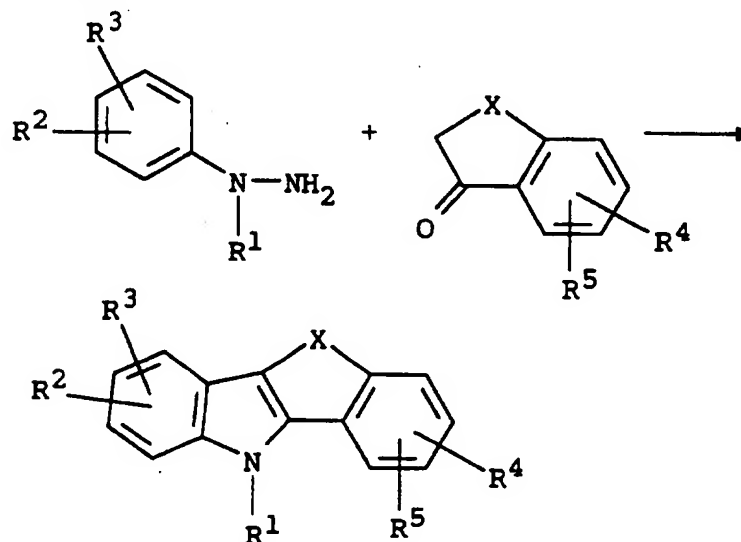
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include methylaminomethyl, ethylaminomethyl, and the like.

The term " Z^{\ominus} " in the above formula is an anion such as perchlorate or halide, for instance chloride, bromide, or the like.

The compounds to be employed in the method of this invention are known. They can be prepared by processes described in the art. For example, United States Patent Number 3,388,133, which is incorporated herein by reference, describes reaction of a phenylhydrazine with a thiochroman-4-one to give compounds of

Formula I wherein X is -CH-S- . This reaction scheme is applicable to other compounds, for example according to the following scheme



The 15-LO inhibitors are effective for treating inflammation and atherosclerosis. A characteristic feature of atherosclerosis is the accumulation of cholesterol ester engorged from foam cells. Foam cells are derived from circulating monocytes which invade artery walls in response to hypercholesterolemia, and mature into tissue macrophages. The enzyme 15-LO has been implicated in inflammatory disorders and in the

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origin and recruitment of foam cells (see Harats, et al., Trends Cardioivasc. Med., 1995;5(1):29-36).

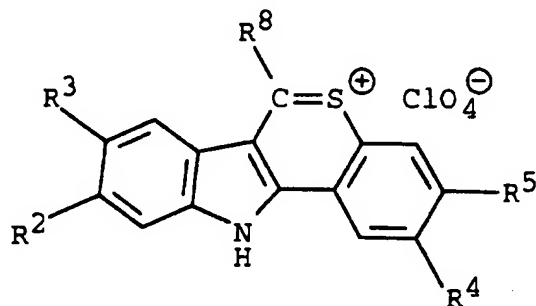
This enzyme is capable of oxidizing esterified polyenoic fatty acids, such as those found in phospholipids. Treatment of experimental animals with antioxidants which reduce hydroperoxides produced by 15-LO has been shown to retard the progression of atherosclerotic lesions. Accordingly, administering compounds which inhibit 15-LO is an effective way to treat and prevent atherosclerosis.

The compounds described above are effective inhibitors of 15-LO when evaluated in standard assays routinely utilized to measure 15-LO activity. Specifically, representative compounds were evaluated by the methods described by Auerbach, et al., Analytical Biochemistry, 1992;201:375-380. Two in vitro assays were utilized, both utilizing rabbit reticulocyte 15-LO, and linoleic acid as substrate, to enzymatically produce a peroxide oxidation product known as 13(S)-HPODE. N-Benzoyl leucomethylene blue was utilized as a colorimetric reagent for detection and quantification of the peroxide formation. Also, HPLC was utilized to quantify the oxidation following incubation at 4°C for 10 minutes.

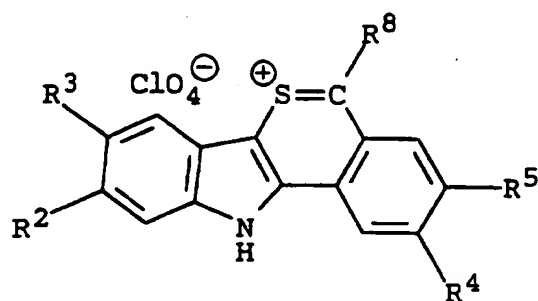
The 15-LO inhibitory activity of representative compounds is presented in Table 1. Data Column 1 gives the concentration of compound required to inhibit 50% of the activity of 15-LO (IC₅₀) when measured by the HPLC method of Auerbach, et al. Data Column 2 gives the concentration of selected compounds to inhibit 50% of the activity of the 5-LO enzyme.

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TABLE 1
Compounds of the Formula



R ²	R ³	R ⁴	R ⁵	R ⁸	15-LO IC ₅₀ μM	5-LO
H	H	H	H	H	1.0-4.0	
H	H	NO ₂	H	H	0.48	>10
H	H	Cl	H	H	12.0	
H	H	CH ₃	H	H	1.9	
H	H	H	CH ₃	H	1.0-4.0	
H	H	-(CH ₂) ₄ -		H	0.5-2.0	>32
H	CH ₃ O-	H	H	H	0.70	>9.6
CH ₃ O	H	H	H	H	26.0	
H	H	H	H	CH ₃	>25	



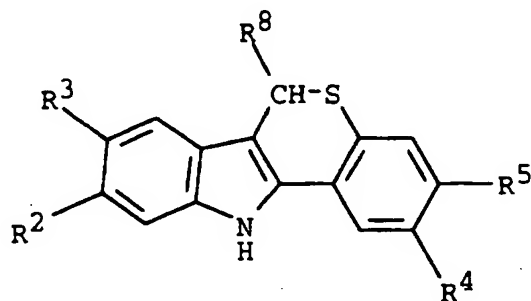
H	H	H	H	H	3.8	22
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TABLE 1 (continued)

R ²	R ³	R ⁴	R ⁵	R ⁸	15-LO IC ₅₀ μM	5-LO
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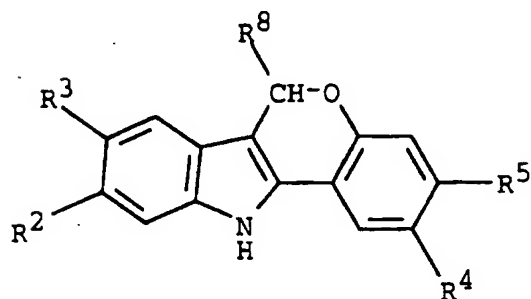
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H	H	H	H	H	1.3	>100
H	CH ₃ O-	H	H	H	0.6	>10
CH ₃ O-	H	H	H	H	4.5	>50

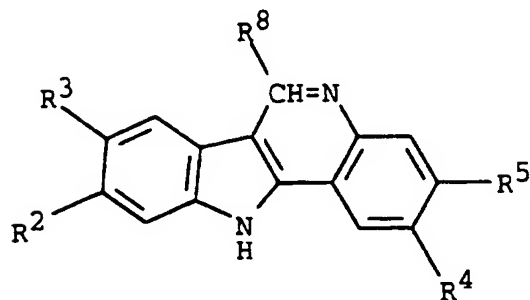
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H	CH ₃ O-	H	H	H	4.0	>50
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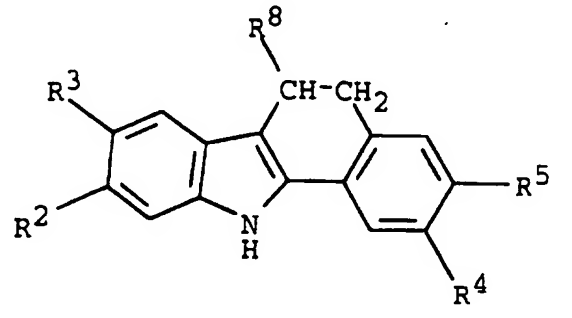
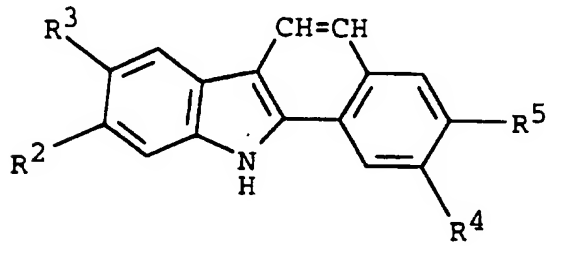
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H	CH ₃ O-	H	H	H	>25 μM	
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TABLE 1 (continued)

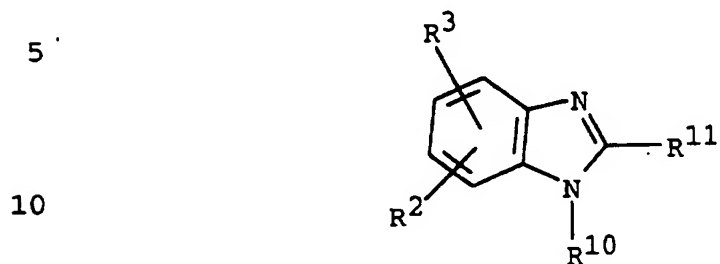
R^2	R^3	R^4	R^5	R^8	15-LO IC ₅₀ μ M	5-LO
<div style="text-align: center;">  </div>						
H	CH ₃ O-	H	H	H	>25 μ M	
<div style="text-align: center;">  </div>						
H	H	H	H	H	1.5	>10

As noted above, benzimidazoles are especially preferred 15-LO inhibitors to be employed in the claimed method. The 15-LO inhibitory activity of typical benzimidazoles are given in Table 2.

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TABLE 2

Compounds of the Formula



	R ²	R ³	R ¹⁰	R ¹¹	15-LO IC ₅₀ μM	5-LO IC ₅₀ μM
15	H	H	H		1.50	>10
	H	5-Cl	H		0.65	>10
	H	5-Cl	H		0.7	>10
	H	5-Cl	H		0.24	>10

20

Styrenes are potent 15-LO inhibitors which can be employed in the present method. Table 3 gives the 15-LO inhibitor of typical styrenes.

25

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TABLE 3

5					
10	R^2	R^3	Het	15-LO IC ₅₀ μ M	5-LO IC ₅₀ μ M
	H	4-OCH ₃		1.6	>10

15 Typical indole 15-LO inhibitors which can be utilized have the activities shown in Table 4.

TABLE 4

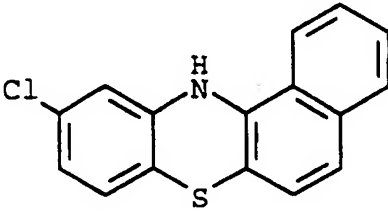
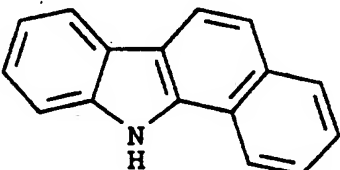
20									
25	R^1	R^2	R^3	R^4	R^5	R^6	Y	15-LO IC ₅₀ μ M	5-LO IC ₅₀ μ M
30	H	H	H	H	3-Cl	H	S	4	>10
	H	H	H	H	H	H	CH ₂	1.5	>10

35 Table 5 gives additional selectivity data for typical 15-LO inhibitors which can be utilized in the method of this invention.

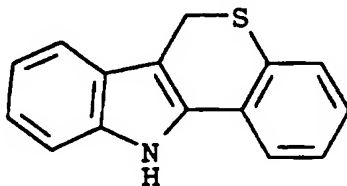
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TABLE 5

		15-LO IC ₅₀ μM	5-LO IC ₅₀ μM
5		2.0	>30
10		1.5	>10
15	CH ₃ (CH ₂) ₃ (CH ₂ -C≡C-) ₄ (CH ₂) ₃ -COOH	0.75	>10

As further evidence of 15-LO inhibitors being effective to prevent and treat inflammation and atherosclerosis in animals, one representative compound has been extensively evaluated in cholesterol-fed rabbits over a 12-week period. The compound evaluated "Compound A" was 6,11-dihydro[1]benzothiopyran[4,3-6]-indole, the compound of Formula I where R¹, R², R³, R⁴, and R⁵ each are hydrogen, and X is -CH₂-S-, i.e.,



Specific pathogen-free New Zealand White rabbits (≈2.5 kg) were obtained from Myrtle's Rabbitry (Thompson Station, TN). The animals were fed a standard laboratory diet (Ralston Purina, St. Louis, MO) and were allowed to become acclimatized for 7 days before initiation of the study, at which time two

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groups of rabbits (n = 10 each) were begun on a diet enriched with cholesterol (0.25% wt/wt), peanut oil (3% wt/wt), and coconut oil (3% wt/wt), with a small amount of applesauce mixed into the food to enhance palatability. This diet was designed to produce a modest hypercholesterolemic response. The control group received no additional treatment. The drug-treated group received 350 mg of Compound A per kilogram body weight per day in their food. Rabbits were permitted access to 40 g of food at ~12 hour intervals via automated feeders, and diet intake was monitored every day such that the animals received 175 mg/kg/bid. Water was available ad libitum. Body weights were measured at regular intervals throughout the 12-week study. Blood samples were obtained at the indicated intervals for determination of hematocrit and plasma lipid concentrations.

Characterization of Atherosclerotic Lesions

Rabbits were euthanized by an overdose of sodium pentobarbital (150 mg/kg⁻¹) and exsanguinated via the abdominal aorta. Aortas were removed from the valve to the ileal bifurcation, opened to expose the intima, and photographed with a Polaroid camera. By use of these photographs, the areas of grossly discernible atherosclerosis were manually integrated on a digitizing pad and calculated with SigmaScan (Jandel Scientific). Aortas were visually subdivided into three areas: arch (aortic valve to first intercostal), thoracic aorta (first intercostal to diaphragm area), and abdominal aorta (diaphragm to ileal bifurcation). In addition to extracting aortas, body tissues were surveyed for indications of adverse reactions.

Determination of Cholesterol Esters and Unesterified Cholesterol Content

-20-

Weighed segments of each aortic region (arch, thoracic, and abdominal) were extracted. Esterified and unesterified cholesterol content of aortic tissue were determined by gas chromatography using 5- α -cholestane as an internal standard.

In the control group, the arch area of aortic sections demonstrated about 15% lesion coverage of intima, whereas those animals receiving Compound A showed no lesion coverage. No detectable lesions were seen in either group in the thoracic region. In the abdominal region, the control group exhibited 5% lesion coverage, whereas the treated group exhibited about 1%. The treated group had no detectable cholesterol esters present in the arch, thoracic, or abdominal regions, whereas the control group had about 2 mg/g tissue wet weight of cholesterol esters in the arch region, none in the thoracic region, and about 0.6 mg/g in the abdominal region. Test animals and the control group had about the same amount of unesterified cholesterol in the thoracic and abdominal regions (0.7-0.8 mg/g tissue wet weight), while in the arch region, the control group had about 1.4 mg/g while the treated group had about 0.8 mg/g.

These data establish that administration of a 15-LO inhibitor effectively protects against the development of atherosclerosis in animals.

In an especially preferred embodiment of this invention, the 15-LO inhibitor utilized is a specific inhibitor of 15-LO. The term "specific" as used herein means that a compound inhibits 15-LO at least about ten-fold (10X) more effectively than it inhibits 5-LO. For example, a preferred group of compounds to be employed in the present method are defined by Formula I. A typical compound from within that group is 6,11-dihydro[1]benzothiopyrano[4,3-b]-indole (Compound A). Its 15-LO inhibitory activity is an IC_{50}

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of 1.3 μM , and its 5-LO inhibitory activity is $>100 \mu\text{M}$. The compound thus inhibits 15-LO at least about 100 times more potently than it inhibits 5-LO. The compound is therefore a "specific" 15-LO inhibitor for purposes of this invention.

Similarly, a preferred benzimidazole to be employed in the invention is 2-(4-chlorophenyl)-5-chlorobenzimidazole. It has a 15-LO IC_{50} of 0.65 μM , and a 5-LO IC_{50} of greater than 10 μM . Accordingly, its 15-LO to 5-LO ratio of activities is greater than 10, thus making the compound a specific 15-LO inhibitor according to this invention.

All that is required to practice this invention is to administer to a mammal an effective amount of any compound that is a 15-LO inhibitor. For example, the compounds of Formula I are useful for treating atherosclerosis and inflammation by virtue of their ability to inhibit 15-LO as established by the data in Table 1. Accordingly, any compound that is determined to inhibit 15-LO in a test system, such as described above, can be employed in this invention.

For use according to this invention, the compounds can be formulated into compositions suitable for administering to animals, including humans, for treating and preventing inflammation and atherosclerosis. The compounds can be formulated for administration by any route, for instance orally, parenterally, topically, and rectally. For oral administration, for example, a 15-LO inhibitor can be mixed with an inert diluent or with an assimilable edible carrier, or it may be enclosed in a hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal

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tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5% to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a therapeutically effective dosage will be obtained.

Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 5 and 1000 mg of active compound, and ideally about 25 to about 750 mg.

The tablets, troches, pills, capsules, and the like may also contain common pharmaceutical excipients such as binders, sweeteners, and the like. Typical binders include gum tragacanth, acacia, corn starch, and gelatin, as well as excipients such as dicalcium phosphate. Typical disintegrating agents include corn starch, potato starch, alginic acid, and the like. A commonly used lubricant is magnesium stearate. Typical sweetening agents are sucrose, lactose, or saccharin, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring can be utilized. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should

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be pharmaceutically pure and substantially nontoxic in the amounts employed.

5 The 15-LO inhibitors can also be formulated for topical administration, for instance as patches, salves, creams, ointments, and the like. Agents commonly utilized to enhance transdermal passage can also be employed. The compounds can also be formulated with waxes and the like for convenient rectal administration.

10 The active 15-LO inhibitor may also be administered parenterally or intraperitoneally. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these
15 preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the
20 extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be
25 preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, and liquid polyethylene
30 glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin; by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. the
35 prevention of the action of microorganisms can be brought about by various antibacterial and antifungal

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agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged
5 absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by
10 incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various
15 sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of
20 preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable
25 carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except
30 insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

35 It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of

-25-

administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined
5 quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms are dictated by and directly dependent on (a) the unique characteristics of the
10 active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired
15 as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed.
20 The term "effective amount" means that quantity of a 15-LO inhibitor which has a positive therapeutic effect for treating or preventing the inflammation or the atherosclerosis which affects the mammal. Such amount is that which inhibits the 15-LO enzyme; in other
25 words, a 15-LO inhibiting amount. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 5 to about 1000 mg, with from about 25 to about 750 mg being preferred. A typical dose will be about 50 to about 500 mg. In the
30 case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients. The unit dosages typically will be administered from one to four times per day, or as
35 otherwise needed to effect treatment of the disease state.

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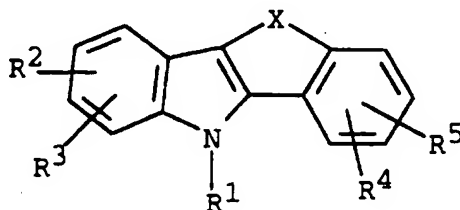
The invention therefore is a method for treating and preventing inflammation and atherosclerosis in mammals. The compounds are effective in inhibiting the activity of 15-LO, and as such can be administered to a mammal, including a human, to effectively diminish and treat atherosclerosis and inflammation. The compounds will be administered at a dose which is effective to treat atherosclerosis, typically from about 1.0 to about 100 mg/kg of body weight of the subject being treated.

The compounds also are useful for treating and preventing inflammation, for example, swelling due to injuries, swelling around bones and joints, and the like. The compounds will be administered to an animal suffering from inflammation in an anti-inflammatory effective amount that is effective to treat the inflammation. Typical doses will be from about 1.0 to about 100 mg/kg of body weight.

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CLAIMS

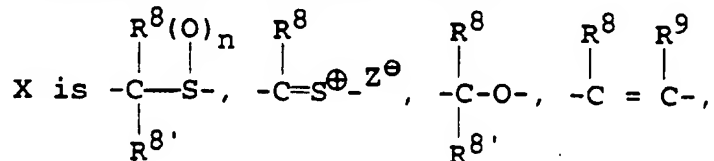
1. A method for treating and preventing inflammation or atherosclerosis in a mammal comprising administering an effective amount of a 15-LO inhibitor.
2. A method according to Claim 1 wherein the 15-LO inhibitor is a specific 15-LO inhibitor.
3. A method for treating and preventing inflammation or atherosclerosis in a mammal comprising administering a 15-LO inhibiting amount of a compound of Formula I



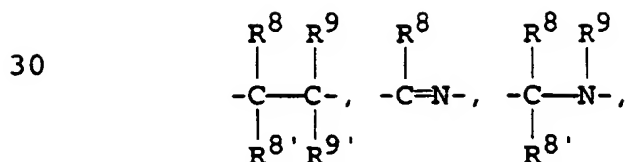
I

wherein:

R^1 is hydrogen or C_1 - C_6 alkyl;
 R^2 , R^3 , R^4 , and R^5 independently are hydrogen, C_1 - C_6 alkyl, nitro, halo, CN, OR^6 , NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, CH_2OR^6 , or $-CH_2NR^6R^7$, and R^2 and R^3 , and R^4 and R^5 , when attached to adjacent ring atoms, can be $-(CH_2)_3$ or 4^- ;
 in which R^6 and R^7 independently are hydrogen, C_1 - C_6 alkyl, phenyl, or benzyl, and when taken together with the nitrogen to which they are attached, R^6 and R^7 can complete a cyclic ring having from 3 to 7 carbon atoms;

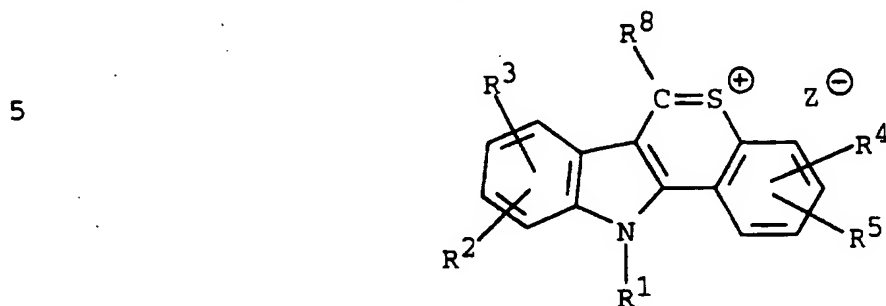


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35 in which R^8 , $\text{R}^{8'}$, R^9 , and $\text{R}^{9'}$ independently are hydrogen or $\text{C}_1\text{-C}_6$ alkyl, n is 0, 1, or 2, and Z^\ominus is an anion, and pharmaceutically acceptable salts thereof.

4. A method according to Claim 3 employing a compound of the formula

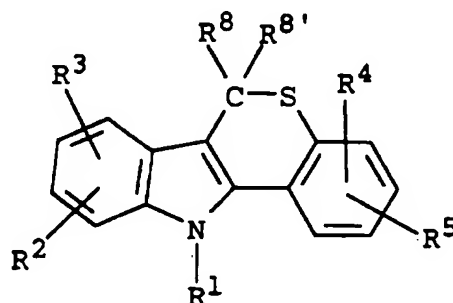


wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and Z^\ominus are as defined above.

5. A method of Claim 4 employing a compound wherein Z^\ominus is ClO_4^\ominus or halo.
6. A method of Claim 5 employing a compound wherein R^8 is hydrogen.
7. A method of Claim 6 employing a compound wherein R^2 and R^3 both are hydrogen.
8. A method of Claim 7 employing a compound wherein R^5 is hydrogen.
9. The method of Claim 8 employing a compound wherein R^4 is NO_2 .

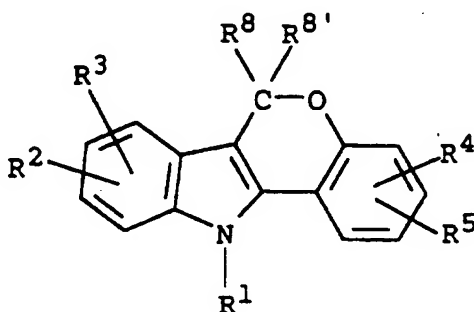
-29-

10. The method of Claim 8 employing a compound wherein R^4 is CH_3 .
11. A method of Claim 4 employing a compound wherein R^2 , R^4 , and R^5 are hydrogen and R^3 is $\text{CH}_3\text{O}-$.
12. A method according to Claim 3 employing a compound having the formula



wherein R^1 , R^2 , R^3 , R^4 , R^5 , and R^8 are as defined above.

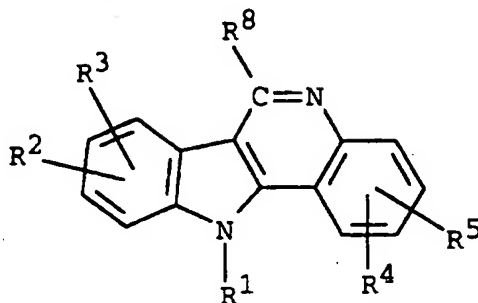
13. A method according to Claim 12 employing a compound wherein R^1 , R^4 , R^5 , and R^8 are hydrogen, R^2 and R^3 independently are hydrogen or $\text{CH}_3\text{O}-$.
14. A method according to Claim 3 employing a compound having the formula



wherein R^1 , R^2 , R^3 , R^4 , R^5 , and R^8 are as defined above.

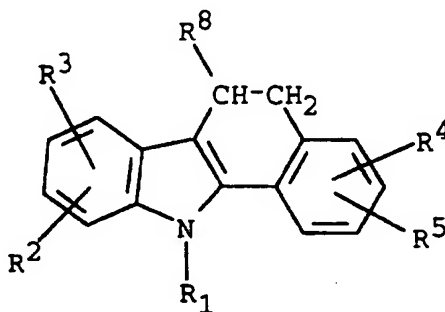
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15. A method according to Claim 3 employing a compound having the formula

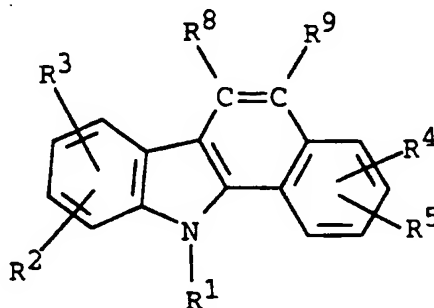


wherein R¹, R², R³, R⁴, R⁵, and R⁸ are as defined above.

16. A method according to Claim 3 employing a compound having the formula



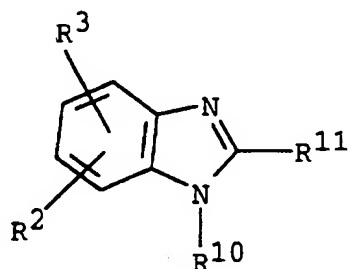
17. A method according to Claim 3 employing a compound having the formula



wherein R¹, R², R³, R⁴, R⁵, and R⁸ are as defined above.

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18. A method for treating and preventing inflammation or atherosclerosis in a mammal comprising administering a 15-LO inhibiting amount of a benzimidazole.
19. A method according to Claim 18 employing a benzimidazole of Formula II



II

wherein:

R^2 and R^3 independently are hydrogen, C_1 - C_6 alkyl, nitro, halo, CN, OR^6 , NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$, and R^2 and R^3 when attached to adjacent ring atoms can be

$-(CH_2)_3$ or 4 ;

R^6 and R^7 are independently hydrogen, C_1 - C_6 alkyl, phenyl or benzyl, and when taken together with the nitrogen to which they are attached, R^6 and R^7 can complete a cyclic ring having from 3 to 7 carbon atoms;

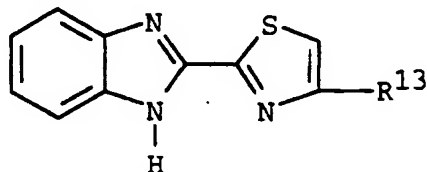
R^{10} is SO_2R^{12} , hydrogen, C_1 - C_6 alkyl, phenyl, or phenyl substituted with 1, 2, or 3 groups selected from halo, CN, OR^6 , C_1 - C_6 alkyl, NR^6R^7 , CO_2R^6 , $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$; and

R^{11} and R^{12} independently are hydrogen, halo, NR^6R^7 , OR^6 , C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl optionally containing an O, N, or S atom, phenyl, or phenyl substituted by 1, 2, or 3 groups selected from halo, CN, OR^6 , C_1 - C_6 alkyl, NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$.

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20. A method according to Claim 19 employing 2-(4-chlorophenyl)-5-chlorobenzimidazole.
21. A method according to Claim 18 employing a benzimidazole of the formula

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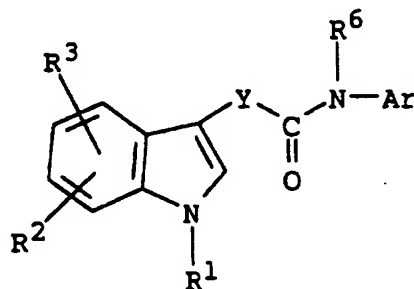


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wherein R^{13} is phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-nitrophenyl, 2,5-dichlorophenyl, 2-furanyl, 2-thienyl, 3-pyridyl, or 4-pyridyl.

22. A method of Claim 21 employing a benzimidazole wherein R^{12} is 2-thienyl.
23. A method according to Claim 1 employing a compound of Formula III

5



III

10

wherein:

- R^1 is hydrogen or C_1-C_6 alkyl;
- R^2 and R^3 independently are hydrogen, C_1-C_6 alkyl, nitro, halo, CN, OR^6 , NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, $-CH_2OR^6$, or $-CH_2NR^6R^7$;
- Y is CH_2 , S, O, or NR^7 ;
- R^6 and R^7 independently are hydrogen, C_1-C_6 alkyl, phenyl or benzyl, or taken together with a

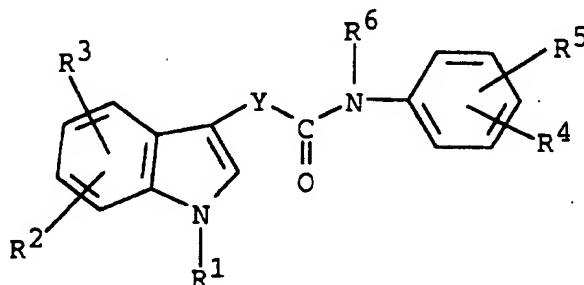
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-33-

20 nitrogen to which they are attached, R^6 and R^7 can complete a cyclic ring having from 3 to 7 carbon atoms; and

25 Ar is phenyl, Het, or phenyl and Het substituted with 1, 2, or 3 groups selected from halo, CN, OR^6 , C_1-C_6 alkyl, NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$.

24. A method according to Claim 23 employing a compound of the formula

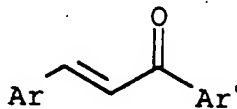


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wherein R^1 , R^2 , R^3 , R^6 , and Y are as defined above, and R^4 and R^5 independently are hydrogen, C_1-C_6 alkyl, nitro, halo, CN, OR^6 , NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, $-CH_2OR^6$, or $-CH_2NR^6R^7$, and R^4 and R^5 , when attached to adjacent ring atoms, can be $-(CH_2)_3$ or 4^- .

15

25. A method according to Claim 1 employing a styrene of the formula



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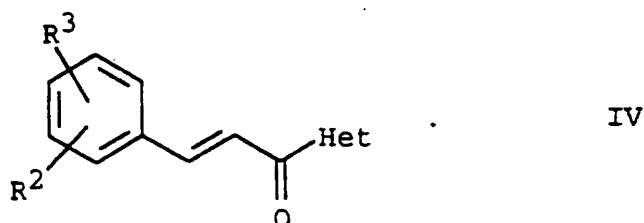
wherein Ar and Ar' independently are phenyl, Het, and phenyl or Het substituted with 1, 2, or 3 groups selected from halo, CN, OR^6 , C_1-C_6 alkyl, NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$, and where Het is a heterocyclic group selected from thiophene, furan, pyrrole, isopyrrole, pyrazole,

10

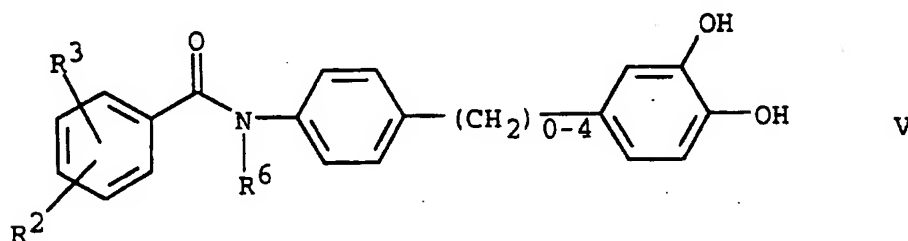
-34-

- 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 1,2,3-oxadiazole, thiazine, pyridine, pyrazine, piperazine, pyrrolidine, piperidine, and pyridazine, and R^6 and R^7 independently are hydrogen, C_1 - C_6 alkyl, phenyl, or benzyl.

26. A method according to Claim 25 employing a styrene having the Formula IV

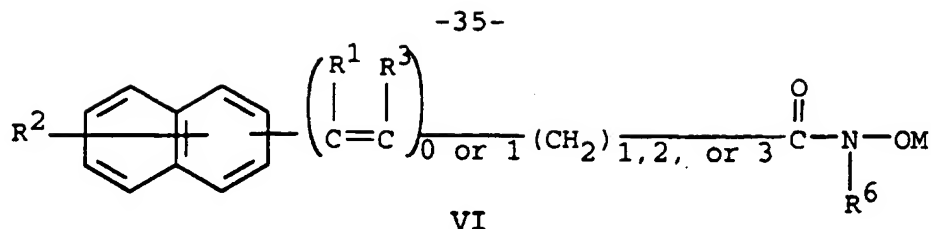


27. A method according to Claim 1 employing a catachol having the Formula V



- 10 wherein R^2 and R^3 independently are hydrogen, C_1 - C_6 alkyl, nitro, halo, CN, OR^6 , NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$; and R^6 and R^7 independently are hydrogen, C_1 - C_6 alkyl, phenyl, or benzyl.

28. A method according to Claim 1 employing a naphthalene of the Formula VI



wherein:

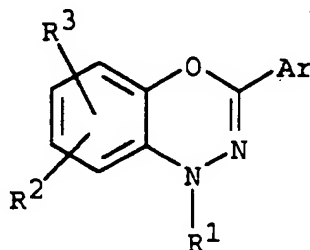
R^1 is hydrogen or C_1 - C_6 alkyl;

R^2 and R^3 independently are hydrogen, C_1 - C_6 alkyl, nitro, halo, CN, OR^6 , NR^6R^7 , CO_2R^6 , $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$;

R^6 and R^7 independently are hydrogen, C_1 - C_6 alkyl, phenyl, or benzyl; and

M is hydrogen or a cation selected from sodium, potassium, and calcium.

29. A method according to Claim 1 employing a compound of Formula VII



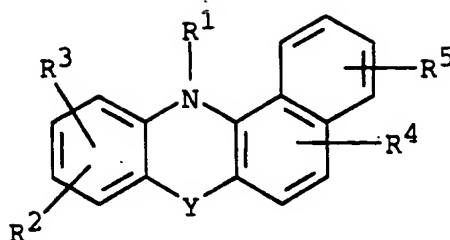
wherein R^1 is hydrogen or C_1 - C_6 alkyl;

R^2 and R^3 independently are hydrogen, C_1 - C_6 alkyl, nitro, halo, CN, OR^6 , NR^6R^7 , CO_2R^6 , $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$;

R^6 and R^7 independently are hydrogen, C_1 - C_6 alkyl, phenyl, or benzyl, and when taken together with the nitrogen to which they are attached, R^6 and R^7 can complete a cyclic ring having from 3 to 7 carbon atoms.

30. A method according to Claim 1 employing a compound of the formula

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wherein:

R^1 is hydrogen or C_1 - C_6 alkyl;

R^2 , R^3 , R^4 , and R^5 independently are hydrogen, C_1 - C_6 alkyl, nitro, halo, CN, OR^6 , NR^6R^7 , $-CO_2R^6$, $CONR^6R^7$, CH_2OR^6 , or $CH_2NR^6R^7$, and R^2 and R^3 , and R^4 and R^5 , when attached to

adjacent ring atoms, can be $-(CH_2)_3$ or 4^- ;

Y is CH_2 , S, O, or NR^7 ;

R^6 and R^7 independently are hydrogen, C_1 - C_6 alkyl, phenyl, or benzyl, and when taken together with the nitrogen to which they are attached, R^6 and R^7 can complete a cyclic ring having from 3 to 7 carbon atoms.

INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/US 96/14242

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/40 A61K31/47 A61K31/415 A61K31/425 A61K31/535
 A61K31/445 A61K31/54 A61K31/495 A61K31/12 A61K31/33
 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 199 153 A (ABBOTT LAB.) 29 October 1986 see page 2, paragraph 2 see page 22; table 2 ---	1,2
Y	TRENDS CARDIOVASC MED, vol. 5, no. 1, January 1995, pages 29-36, XP000610711 HARATS ET AL.: "a possible role for 15-lipoxygenase in atherogenesis" see page 33 - page 34 --- -/-	1,2

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

29 January 1997

Date of mailing of the international search report

31. 01. 97

Name and mailing address of the ISA

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Authorized officer

Trifilieff-Riolo, S

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 96/14242

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TRENDS BIOCHEM SCI, vol. 16, no. 10, 1991, pages 369-374, XP000611639 SCHEWE ET AL.: "do 15-lipoxygenases have a common biological role?" see page 372, right-hand column, line 56 - line 59 see page 373, paragraph 2 ---	1,2
Y	PROC NATL ACAD SCI USA, vol. 89, no. 1, 1992, pages 217-221, XP000611631 CONRAD ET AL.: "specific inflammatory cytokines regulate the expression of human 15-lipoxygenase" abstract see page 217, left-hand column, paragraph 2 ---	1,2
X	EP 0 178 413 A (BEECHAM GROUP PLC) 23 April 1986 page 2, paragraph 2 and examples ---	18,19
X	EP 0 419 210 A (PFIZER) 27 March 1991 see page 3, line 1 - line 3 compounds 8 and 11 on page 9 ---	18,19
X	EP 0 249 407 A (PFIZER) 16 December 1987 page 2, lines 3-5 and examples 25-27 ---	18
X	EP 0 248 736 A (ROUSSEL UCLAF) 9 December 1987 page 3, lines 41-42 and page 5, Table 1 ---	18
A	US 4 797 495 A (BAIR K.W.) 10 January 1989 cited in the application ---	1-17
A	US 3 388 133 A (YOUNG T.E., SCOTT P.H.) 11 June 1968 cited in the application ---	1-17
A,P	WO 96 03375 A (SCHERING A.G.) 8 February 1996 -----	1-17

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/14242

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 1-17
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: 1,2,18,19
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
In view of the large number of compounds which are defined by the wording
of the claims, the search has been performed on the general idea and
compounds mentioned in the examples of the description.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See next page

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:

See next page

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

subject 1: claims 1 and 2 (both partially) and claims 3 to 17: use of a tetracyclic indole of formula I to treat or prevent inflammation or atherosclerosis
subject 2: claims 1 and 2 (both partially) and claims 18 to 22: use of benzimidazole of formula II for the same purposes (as far as not comprised in subject 1)
subject 3: claims 1 and 2 (both partially) and claims 23 and 24: use of a compound of formula III for the same purposes (as far as not comprised in subject 2)
subject 4: claims 1 and 2 (both partially) and claims 25 and 26: use of a styrene for the same purposes (as far as not comprised in subject 3)
subject 5: claims 1 and 2 (both partially) and claim 27: use of a catechol of formula V for the same purposes (as far as not comprised in subject 4)
subject 6: claims 1 and 2 (both partially) and claim 28: use of a naphthalene of formula VI for the same purposes (as far as not comprised in subject 5)
subject 7: claims 1 and 2 (both partially) and claim 29: use of a compound of formula VII for the same purposes (as far as not comprised in subject 6)
subject 8: claims 1 and 2 (both partially) and claim 30: use of a heterocyclic compound of formula as described in said claim for the same purposes (as far as not comprised in subject 7)

Only the first and second subjects were searched.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/14242

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INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 96/14242

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		AU-A- 3254595	22-02-96
